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Enantioselective Aza-Henry Reaction Catalyzed by a Bifunctional Organocatalyst

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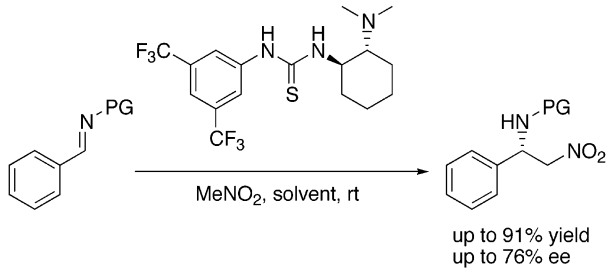
ABSTRACT



The aza-Henry reaction of imines with nitroalkanes was promoted by chiral thiourea with an *N*,*N*-dimethylamino group to give *β*-nitroamines with good enantioselectivity. Various *N*-protected imines were examined as substrates. *N*-Phosphinoylimine gave the best result in terms of chemical yield and enantioselectivity (up to 91% yield, up to 76% ee).

The aza-Henry reaction, the nucleophilic addition of nitroalkanes to imines to give *β*-nitroamine derivatives, is a useful carbon−carbon bond-forming process in organic chemistry. The diversity of the transformations of the *β*-nitroamines, such as reduction to 1,2-diamines[1] and Nef reaction to α-amino acids,[2] provides numerous applications of this process.[3−6] The enantioselective version of this reaction was not known until quite recently.[7−10] To the best of our knowledge, there were only two groups that had reported on catalytic asymmetric aza-Henry reaction and all of the reactions reported were metal-catalyzed. Shibasaki et al. reported that heterobimetallic complexes with lanthanide BINOL systems promoted the aza-Henry reaction to give *β*-nitroamines with high enantioselectivity.[9] Jørgensen et al. also developed a catalytic asymmetric version of this reaction with bisoxazoline copper(II) complexes.[10]

Although urea derivatives are known to act as acid catalysts in several reactions,[11] enantioselective reactions were rare (Figure 1).[12] We have recently reported novel

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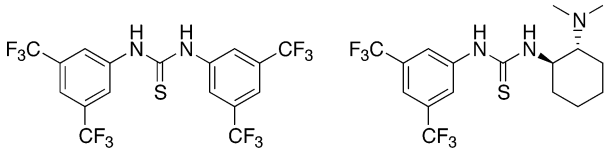

Figure 1. Structure of thiourea derivatives.

thiourea derivatives with several tertiary amino groups, which act as bifunctional organocatalysts on enantioselective Michael reaction of malonates to nitroolefins.[13] In this reaction, the thiourea seems to interact with a nitro group of the nitroolefins and enhance electrophilicity of nitroolefins (Figure 2).[14]

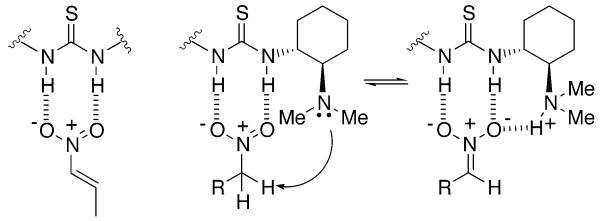

Figure 2. Working hypothesis.

Hence, we expected that the corresponding nitronate could be produced from nitroalkane with the bifunctional thiourea via the hydrogen-bonding activation with the thiourea moiety and subsequent deprotonation by the neighboring tertiary amino group. If so, the catalyst would promote the asymmetric aza-Henry reaction (eq 1). Herein we report the first enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst.

We first investigated the racemic reaction of imines **2a**−**c** bearing various protecting groups (PG) with nitromethane **4a** in the presence of Et_3N (TEA) and thiourea **1a** (Table 1). The reaction of *N*-phenylimine **2a** with 0.1 equiv of TEA afforded no desired *β*-nitroamine **3a** due to the low reactivity of **2a** (entry 1). On the other hand, subjection of *N*-tosylimine **2b** under the same reaction conditions gave *β*-nitroamines **3b**[15] in good yield (entry 2, 74%). In the case of *N*-phosphinoylimine **2c**,[16] the desired adduct **3c** was obtained in 57% yield in the presence of 0.1 equiv of TEA, while

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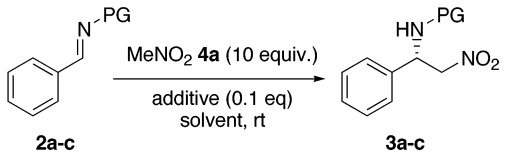
Table 1. Effect of Thiourea Catalysts[a]

entry	PG	additive	adduct	yield[b] (%)
1	Ph (**2a**)	TEA	**3a**	0
2	Ts (**2b**)	TEA	**3b**	74
3	$P(O)Ph_2$ (**2c**)	TEA	**3c**	57
4	$P(O)Ph_2$ (**2c**)	**1a**	**3c**	0
5	$P(O)Ph_2$ (**2c**)	TEA + **1a**	**3c**	49

[a] Reaction was conducted with additive (0.1 equiv), **4a** (10 equiv), and CH_2Cl_2 at room temperature for 24 h. [b] Isolated yield.

treatment of **2c** with thiourea **1a** did not give **3c** at all. Then, with the expectation that coexistence of TEA and **1a** would promote the generation of the nitrate anion from **4a**, the reaction of **2c** was carried out in the presence of TEA and **1a**, but **3c** was only obtained in moderate yield (49%, entry 5).



(eq 1)

This result indicates that the thiourea and amine seem to mutually weaken their reactivities. However, the bifunctional thiourea **1b**, whose amino group and thiourea moiety are located in appropriate positions, can be used for this purpose (Figure 2). Hence, we investigated the reaction of imines **2a**−**c** with nitromethane **4a** in the presence of bifunctional organocatalyst **1b**[13] (Table 2, entries 1−3). In practice,

Table 2. Optimization of Reaction Conditions[a]

entry	PG	solvent	adduct	time (h)	yield[b] (%)	% ee[c] (config[d])
1	Ph (**2a**)	CH_2Cl_2	**3a**	24	e	e
2	Ts (**2b**)	CH_2Cl_2	**3b**	4.5	99	4 (−)[e]
3	$P(O)Ph_2$ (**2c**)	CH_2Cl_2	**3c**	24	87	67 (*S*)
4	$P(O)Ph_2$ (**2c**)	MeCN	**3c**	48	e	e
5	$P(O)Ph_2$ (**2c**)	MeOH	**3c**	48	44	33 (*S*)
6	$P(O)Ph_2$ (**2c**)	toluene	**3c**	140	47	62 (*S*)
7	$P(O)Ph_2$ (**2c**)	THF	**3c**	48	43	75 (*S*)
8	$P(O)Ph_2$ (**2c**)	dioxane	**3c**	75	73	76 (*S*)

[a] Reaction was conducted with **1b** (0.1 equiv), **4a** (10 equiv), and several solvents at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **3b** and **3c** using a chiral column. [d] Absolute configuration was determined by comparison of the HPLC retention time with that of literature data.[9a] [e] Not determined.

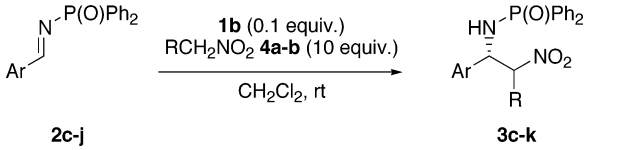
whereas the reaction of **2a** in CH_2Cl_2 afforded no desired *β*-nitroamines **3a**, **2b** and **2c** reacted with nitromethane efficiently to give the desired adducts **3b** and **3c** in good yield (entries 1−3). In the case of **2c**, the enantioselectivity of the adduct **3c** was 67% ee, while **2b** gave an almost

racemic adduct **3b**. The enantiomeric excess was determined by HPLC analysis of **3c** using a chiral column, and the absolute configuration of **3c** was determined by comparison of the HPLC retention time with that of literature data. We selected **2c** as a substrate and optimized the reaction solvent. The adduct **3c** was negligibly obtained or obtained with low enantioselectivity in a polar solvent (MeCN, MeOH), since these solvents probably inhibit hydrogen-bonding interaction between nitromethane **4a** and the thiourea moiety of **1b** (Table 1, entries 4 and 5). In contrast, nonpolar solvents such as toluene provided **3c** with good enantioselectivities (62% ee, entry 6), while the reaction rate decreased dramatically. On the other hand, when the reaction was carried out in ether solvents (THF or 1,4-dioxane), the adduct **3c** was obtained with up to 76% ee after a slightly prolonged reaction time (75 h, entries 7 and 8).

We examined the reaction of various phosphinoylimines **2c**−**j** with nitroalkanes **4a** and **4b** in CH_2Cl_2 due to the reasonable reaction rate. Table 3 summarizes the results of the reactions. In all cases, the corresponding β-nitroamines **3c**−**j** were obtained in good yields with moderate to good enantioselectivities. Introduction of electron-donating or electron-withdrawing groups on the aromatic ring of imines did not affect the enantioselectivities (entries 1−3). When sterically hindered imine **2f** was used as a substrate, the enantioselectivity of the adduct **3f** slightly increased (70% ee, entry 4). Similarly, imines **2g**−**i** possessing a heteroaromatic ring provided β-nitroamines with good enantioselectivities (64−76% ee, entries 5−7). The same reaction of imine **2j**, prepared from cinnamylaldehyde, proceeded regioselectively to give the 1,2-addition adduct **3j** as the single product with moderate stereoselectivity (entry 8). Finally, we examined enantio- and diastereoselective aza-Henry reaction of **2c** with nitroethane **4b** in the presence of **1b** (entry 9). When nitroethane **4b** was reacted with imine **2c** under the same reaction conditions, the corresponding desired products **3k** were obtained as a diastereomixture (the ratio of 3:1), while the enantioselectivity of the major diastereomer was kept to a good level (67% ee).

In summary, thiourea **1b** worked well as a chiral organocatalyst in the aza-Henry reaction of various phosphinoylimines with nitroalkanes, and gave the β-nitroamines with moderate to good enantioselectivity. This is the first example of enantioselective aza-Henry reaction with an organocatalyst. Further investigations to improve the enantioselectivity with other thiourea catalysts are under way in these laboratories.

Table 3. Aza-Henry Reaction of *N*-Phosphinoylimines Catalyzed by Bifunctional Organocatalyst[a]



2c-j **3c-k**

entry	Ar	**4** (R)	adduct	yield[b] (%)	% ee[c] (dr[d])
1	Ph (**2c**)	H	**3c**	87	67
2	4-MeC_6H_4 (**2d**)	H	**3d**	72	63
3	4-ClC_6H_4 (**2e**)	H	**3e**	76	67
4	2-naph (**2f**)	H	**3f**	78	70
5	2-furyl (**2g**)	H	**3g**	85	76
6	2-pyridyl (**2h**)	H	**3h**	91	68
7	2-thieny (**2i**)	H	**3i**	57	64
8	cinnamyl (**2j**)	H	**3j**	68	65
9	Ph (**2c**)	Me	**3k**	83	67[e] (73/27)

[a] Reaction was carried out with **1b** (0.1 equiv), **4a** or **4b** (10 equiv), and CH_2Cl_2 at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **3c**−**k** using a chiral column. [d] Diastereomeric ratio was determined by ^1H NMR. [e] Major diastereomer.

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Supporting Information Available: Experimental procedures and spectroscopic data for products **3c**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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